# Proposed Decision Memo for Aprepitant for Chemotherapy -Induced Emesis (CAG-00248N)

## Decision Summary

CMS is seeking public comment on our proposed determination that there is sufficient evidence to conclude that the use of the oral anti-emetic three drug combination of aprepitant (Emend®), a 5-$HT_3$ antagonist, and dexamethasone is reasonable and necessary for a specified patient population.

For purposes of this proposed determination we are defining the patient population for which the use of the oral anti-emetic three drug combination of aprepitant (Emend®), a 5-$HT_3$ antagonist, and dexamethasone is reasonable and necessary as only those patients who:

- Are receiving anti-cancer chemotherapeutic agents defined as level 5 on Hesketh's classification system of acute emetogenicity of anti-cancer chemotherapeutic agents, and
- Have demonstrated unresponsiveness to other anti-emetic regimens not containing aprepitant that are consistent with nationally recognized guidelines associated with prior administration of the same chemotherapy.

We are requesting public comments on this proposed determination pursuant to section 731 of the Medicare Modernization Act. After considering the public comments and any additional evidence we will make a final determination and issue a final decision memorandum.

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## Proposed Decision Memo

To: Administrative File: CAG #00248
Aprepitant for Chemotherapy-Induced Emesis

From:

Steve Phurrough, MD, MPA

Director, Coverage and Analysis Group

Louis Jacques, MD
Division Director

Karen Daily, MS
Lead Analyst

James A. Rollins, MD PhD MSHA
Lead Medical Officer

Suject: Proposed Coverage Decision Memorandum for Aprepitant for Chemotherapy-Induced Emesis

Date: January 6, 2005

## I. Proposed Decision

CMS is seeking public comment on our proposed determination that there is sufficient evidence to conclude that the use of the oral anti-emetic three drug combination of aprepitant (Emend®), a 5-$HT_3$ antagonist, and dexamethasone is reasonable and necessary for a specified patient population.

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- Have demonstrated unresponsiveness to other anti-emetic regimens not containing aprepitant that are consistent with nationally recognized guidelines associated with prior administration of the same chemotherapy.

We are requesting public comments on this proposed determination pursuant to section 731 of the Medicare Modernization Act. After considering the public comments and any additional evidence we will make a final determination and issue a final decision memorandum.

## II. Background

*Epidemiology*

Chemotherapy induced nausea and vomiting (CINV) can range from mild to severe, with the most severe cases resulting in dehydration, malnutrition, metabolic imbalances, and potential withdrawal from future chemotherapy treatments. The incidence and severity of CINV are influenced by the specific chemotherapeutic agent(s) used; dosage, schedule and route of administration; and drug combinations. Patient specific risk factors such as sex, age, history of motion sickness, and prior exposure to chemotherapeutic agents can also have an effect on CINV incidence and severity. Men have a lower risk of emesis than women, as do patients over 50 years of age. It is estimated that in the United States, 61% of all cancers occur in patients 65 years of age and older. Approximately 70% to 80% of all cancer patients receiving chemotherapy experience emesis (Kovac 2003, NCCN 2004). Progress has been made in reducing CINV, although it can still be hard to control symptoms that occur more than a day after chemotherapy, during repeat cycles of chemotherapy, and when chemotherapy is given on more than one day or in very high doses.

*Disease Process*

CINV is commonly classified as acute, delayed, anticipatory, breakthrough, or refractory. Acute emesis usually occurs within the first 24 hours after chemotherapy administration, although CINV following highly emetic anti-cancer drugs may last up to 36 hours (ASHP 1999). Delayed emesis develops in patients more than 24 hours after chemotherapy administration. Anticipatory emesis occurs before the patient receives chemotherapy, generally as a conditioned response from a previous negative experience with chemotherapy. Breakthrough emesis occurs in spite of prophylactic treatment and is treated with rescue therapy. Refractory emesis occurs during subsequent chemotherapy cycles when anti-emetic and/or breakthrough therapy has failed (NCCN 2004).

*Interaction of the Intervention with the Disease Process*

There are several mechanisms by which chemotherapeutic agents cause nausea and vomiting, including activation of the chemoreceptor trigger zone (CTZ), stimulation of the gastrointestinal (GI) tract, vestibular mechanisms, and alterations in taste and smell. The CTZ is located in the area postrema of the brain and it is thought that chemotherapy leads to the release of various neurotransmitters that activate the CTZ. Some of the neurotransmitters that may play a role in the expression or control of CINV include dopamine, serotonin, histamine, norepinephrine, arginine vasopressin, angiotensin II, VIP, gastrin, and substance P. Many effective anti-emetics function by inhibiting the release of these neurotransmitters or blocking them from activating receptors. The anti-emetic activity of metoclopramide, for example, is thought to be partly due to its action as a dopamine antagonist. Dexamethasone, an effective anti-emetic, may work by reducing arginine vasopressin levels.

Some believe that chemotherapy leads to a release of serotonin from the gastrointestinal (GI) tract, which then activates the vagus and splanchnic nerves as well as the area postrema of the brain, ultimately leading to emesis. 5-$HT_3$ antagonists may control emesis by preventing serotonin from binding to this 5-$HT_3$ receptor, thereby limiting this emetic cascade.

Substance P is a neuropeptide found in the GI tract as well as in the CTZ. Aprepitant is thought to exert its anti-emetic effect by binding to the NK1 receptor and preventing activation by substance P.

*Treatment Options*

No single anti-emetic agent is completely effective in all patients. As noted above, many factors influence the incidence and severity of CINV, with the specific chemotherapeutic agent as the primary factor to consider when deciding which anti-emetic to administer. Knowledge of the usual degree of emesis after administration of a specific chemotherapeutic agent aids in the most appropriate selection and dosage schedule of anti-emetic agents. Hesketh developed a 5-level classification system of acute emetogenicity of anti-cancer chemotherapeutic agents:

- level 1 (less than a 10% frequency of emesis),
- level 2 (10-30% frequency),
- level 3 (30-60% frequency),
- level 4 (60-90% frequency), and
- level 5 (more than a 90% frequency of emesis).

Algorithms have been developed to define the emetogenicity of individual and combination chemotherapeutic regimens (ASHP 1999, NCCN 2004). Prior to FDA approval of aprepitant, the use of a 5-$HT_3$ antagonist and a corticosteroid was generally considered the standard of care for the prevention of acute chemotherapy-induced emesis (ASCO 1999). However, it is recognized by the medical community that the standard anti-emetic therapy is not effective in preventing acute emesis in all patients receiving highly emetogenic chemotherapy.

**III. History of Medicare Coverage**

Medicare is a defined benefit program. An item or service must fall within a benefit category as a prerequisite to Medicare coverage. § 1812 (Scope of Part A); § 1832 (Scope of Part B) § 1861(s) (Definition of Medical and Other Health Services).

Medicare Part B generally does not cover drugs and biologicals that are usually self-administered, unless expressly authorized by statute. Section 4557 of the Balanced Budget Act (BBA) of 1997 amended §1861(s)(2) of the statute and the definition of "medical and other health services" to include coverage of oral anti-emetic drugs under the conditions specified below:

"an oral drug (which is approved by the Federal Food and Drug Administration) prescribed for use as an acute anti-emetic used as part of a chemotherapeutic regimen if the drug is administered by a physician (or as prescribed by a physician) –

i. for use immediately before, at, or within 48 hours after the time of the administration of the anticancer chemotherapeutic agent; and
ii. as a full replacement for the anti-emetic therapy which would otherwise be administered intravenously." Social Security Act § 1861(s)(2)(T)

In 1999, section 2049 of the Medicare Carrier Manual and section 3112.5 of the Medicare Intermediary Manual (now chapter 15, section 50.5.4, of the Medicare Benefit Policy Manual) were modified to provide coverage of more than one oral anti-emetic for concurrent use, if more than one oral drug is needed to fully replace the intravenous anti-emetic drugs that would otherwise be given for use as part of a chemotherapeutic regimen.

Previous agency statements regarding aprepitant indicated that the drug did not meet the statutory definition of an oral drug under section 1861(s)(2)(T)(ii) of the Social Security Act because a covered oral anti-emetic drug should fully replace the anti-emetic drugs(s) administered intravenously. If one or more conditions or patient populations can be identified for which aprepitant alone or in combination is a full replacement for the anti-emetic drugs(s) administered intravenously, aprepitant may fall under the benefit category specified under section 1861(s)(2)(T)(ii).

## IV. Timeline of Recent Activities

| | |
|---|---|
| July 6, 2004 | CMS opened an internally generated national coverage determination (NCD) review to determine if aprepitant is full replacement for other covered treatment(s) for chemotherapy-induced emesis. If aprepitant is determined to be full replacement, CMS will describe the circumstances where it is reasonable and necessary for Medicare beneficiaries. |
| | The initial 30-day public comment period began. |
| August 6, 2004 | End of public comment period. Eight comments received. |

## V. FDA Status

The FDA approval letter for new drug application (NDA) 21-549, dated September 27, 2002, included the following language:

“This new drug application provides for the use of EMEND® (aprepitant) Capsules in combination with other anti-emetic agents, for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin.”

## VI. General Methodological Principles

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve net health outcomes for patients. Improved net health outcomes is one of several considerations in determining whether an item or service is reasonable and necessary. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.

A detailed account of the methodological principles of study design that agency staff utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A.

## VII. Evidence

### A. Introduction

We are providing a summary of the evidence we considered during our review. We will, of course, consider additional evidence submitted through the public comment period. The evidence reviewed to date in this proposed NCD includes the published medical literature on pertinent clinical trials of aprepitant.

The principal outcome of interest in assessing the efficacy of an anti-emetic drug such as aprepitant is the reduction of nausea and vomiting associated with the administration of chemotherapy. Several means are used to measure control of nausea and vomiting. Vomiting is most simply and objectively measured by counting incidents of emesis. Nausea is more subjective and is measured by questionnaire or through a visual analog scale, where the complete absence of nausea is represented at one end of a line and the worse imaginable nausea is represented at the other end and the subject selects the point on the line that best corresponds to his or her own experience. The impact of chemotherapy-induced nausea and vomiting on normal functioning and quality of life can also be assessed by questionnaire.

The choice of outcome measure depends on the therapeutic goal. Clinical trials of aprepitant used a composite measurement. Subjects were considered to have had a complete response only if there was no vomiting and no use of rescue medications. If, in addition to a complete response, there was no more than minimal nausea then subjects were said to have achieved complete control.

For purposes of this NCD review we are analyzing studies in which anti-cancer drugs identified as highly emetogenic, i.e., Level 5 of Hesketh's 5-level classification system of acute emetogenicity of anti-cancer chemotherapeutic agents, were administered to patients.

The purpose of this analysis is to determine the circumstances under which the use of aprepitant alone or in combination fully replaces intravenous anti-emetic therapy that would otherwise be given and the circumstances under which such use is reasonable and necessary.

**B. Discussion of evidence reviewed**

## 1. Questions

Because aprepitant is a self-administered oral agent, the Medicare program can cover this drug only if it functions alone or in combination with other oral anti-emetics as a full replacement for the intravenous anti-emetic drugs that would otherwise be given. Making this determination requires analysis of two different criteria for success. Aprepitant is not available as an intravenous formulation. Therefore, for aprepitant when used alone as a single agent to be considered as a full replacement for intravenously administered 5-$HT_3$ antagonists and corticosteroids, the focus must be on achieving at least the same level of reduction of nausea and vomiting as the standard oral anti-emetic regimen of a 5-$HT_3$ antagonist and corticosteroid. Alternatively, if the addition of aprepitant to the standard regimen of a corticosteriod and 5-HT3 antagonist is to be considered a full replacement, the focus must be on achieving a responsiveness in patients who would fail on the standard oral anti-emetic therapy.

The questions below address the conditions under which aprepitant may be considered as a full replacement for intravenous anti-emetic therapy which would otherwise be administered and the circumstances under which such use may be reasonable and necessary.

1. *Is the quality of evidence adequate to conclude that aprepitant can function alone as a full replacement to intravenous anti-emetics and is reasonable and necessary for those Medicare patients who are receiving highly emetogenic chemotherapy?*

2. *Is the quality of evidence adequate to conclude that aprepitant can function in combination with other oral anti-emetics as a full replacement to intravenous anti-emetics and is reasonable and necessary for those Medicare patients who are receiving highly emetogenic chemotherapy and who would fail on the standard oral anti -emetic therapy?*

## 2. External technology assessments

We did not request an external technology assessment on this issue and are unaware of any assessments that were conducted independently.

## 3. Internal technology assessments

*Literature search methods*

Medical literature was identified using the Entrez-PubMed database of the National Library of Medicine. The phrases, “aprepitant” and “neurokinin antagonist and cancer”, were used to identify relevant clinical trials. We identified eight papers that met these criteria.

*Evidence Review*

1. *Is the quality of evidence adequate to conclude that aprepitant can function alone as a full replacement to intravenous anti-emetics and is reasonable and necessary for those Medicare patients who are receiving highly emetogenic chemotherapy?*

There are two published clinical trials (Campos, 2001 and van Belle, 2002) that substitute aprepitant for a 5-$HT_3$ antagonist when the 5-$HT_3$ antagonist is used with dexamethasone as part of the standard regimen for prophylaxis of cisplatin chemotherapy-induced vomiting.

The study by Campos et al. was a multicenter, double blind, parallel-group trial in which 351 cisplatin-naïve patients were evaluated for the prevention of acute (0 to 24 hours) and delayed emesis (days 2 to5) after cisplatin (> 70 mg/$m^2$). Patients were randomized to four groups as outlined in Table 1. All patients also received dexamethasone (20 mg PO) before cisplatin. Additional medication was available to treat emesis or nausea at any time. As Group II represented a combination of aprepitant with granisetron, rather than a substitution, its results are not relevant to this question. For the other groups in the acute period, 57%, 46%, and 43% of patients were without emesis in groups I, III, and IV, respectively.

**Table 1. Study by Campos et al.**

| Treatment | | | | No Emesis | |
|---|---|---|---|---|---|
| Group | Evening Prior | Day 1 | Days 2-5 | Day 1 | Days 2-5 |
| I | Placebo | Granisetron | Placebo | 57 % | 29 % |
| II | Placebo | Granisetron + Aprepitant | Aprepitant | 80 % | 63 % |
| III | Aprepitant | Aprepitant | Aprepitant | 46 % | 51 % |
| IV | Placebo | Aprepitant | Aprepitant | 43 % | 57 % |

The primary comparability hypothesis of the trial was the comparison between groups III and I. In this comparison, a 90% confidence interval for the difference was calculated as -24% to 2%, indicating that the two treatments were not comparable as predefined and suggests that the control of acute emesis with aprepitant plus dexamethasone could be less than that with granisetron plus dexamethasone. When group I is compared with groups III and IV combined, the difference has borderline statistical significance (p= 0.04 for a one-sided test of non-inferiority). In the delayed period, the proportions of patients without emesis in groups I, III, and IV were 29%, 51%, and 57%, respectively ($p < 0.01$ for groups III and IV vs. group I). The authors concluded that once daily oral administration of aprepitant was effective in reducing delayed emesis and nausea after high-dose cisplatin but the combination of the $5HT_3$ antagonist plus dexamethasone was numerically superior to aprepitant plus dexamethasone in reducing acute emesis.

Van Belle et al. conducted a multicenter, double-blind, randomized active agent-controlled study of 177 cisplatin-naïve patients with malignant disease. On Day 1, aprepitant was given intravenously as its water-soluble prodrug. All patients received 20 mg of dexamethasone intravenously and 70mg/$m^2$ or more of cisplatin on Day 1. Patients were randomized to three groups. Group I received 100 mg of the aprepitant prodrug intravenously on Day 1 followed by 300 mg of aprepitant orally on Days 2-5. Group II received 100 mg of the aprepitant prodrug intravenously on Day 1 followed by placebo on Days 2-5. Group III received 32 mg of ondansetron intravenously on Day 1 followed by placebo on Days 2-5. The primary efficacy parameters of interest were the proportion of patients without emesis and the proportion without emesis or rescue therapy on Day 1 (acute phase) and on Days 2-5 (delayed phase).

**Table 2. Study by Van Belle et al.**

| Treatment | | | Complete Response | | No Emesis | |
|---|---|---|---|---|---|---|
| Group | Day 1 | Days 2-5 | Day 1 | Days 2-5 | Day 1 | Days 2-5 |
| I | Aprepitant | Aprepitant | 44 % | 59 % | 49 % | 65 % |
| II | Aprepitant | Placebo | 36 % | 46 % | 47 % | 61 % |

| Table 2. Study by Van Belle et al. | | | | | | |
|---|---|---|---|---|---|---|
| III | Ondansetron | Placebo | 83 % | 38 % | 84 % | 41 % |

The results are outlined in Table 2. On Day 1, the proportions of patients with complete response (no emesis and no use of rescue medication) were 44% of patients in Group I, 36% of patients in Group II (40% in Groups I and II combined), and 83% in Group III ($p < 0.01$ for Group III vs. the combined Groups I and II). The proportions of patients with complete response on Days 2-5 were 59% of patients in Group I, 46% of patients in Group II and 38% of patients in Group III ($p < 0.05$ for Group I vs. Group III).

The proportions of patients with no emesis on Day 1 were 49% in Group I, 47% in Group II, and 84% in Group III ($p < 0.01$ for Group I or Group II vs. Group III). On Days 2-5, however, the proportions of patients with no emesis were 65% in Group I, 61% in Group II, and 41% in Group III ($p < 0.05$ for Group I or Group II vs. Group III). Nausea scores in the acute phase were lower for Group III than for Group I, Group II, or Groups I and II combined ($p < 0.05$), although there was no significant difference among groups either for the delayed phase or overall.

The authors concluded that although the combination of the aprepitant prodrug and dexamethasone reduced acute emesis relative to historic rates, it was inferior to the combination of ondansetron and dexamethasone. For the control of delayed emesis, the combination of aprepitant and dexamethasone was superior to ondansetron and dexamethasone.

2. *Is the quality of evidence adequate to conclude that aprepitant can function in combination with other oral anti-emetics as a full replacement to intravenous anti-emetics and is reasonable and necessary for those Medicare patients who are receiving highly emetogenic chemotherapy and who would fail on the standard oral anti -emetic therapy?*

This question requires an evaluation of the effect of the addition of aprepitant to the standard regimen of a 5-$HT_3$ antagonist plus dexamethasone in comparison to the standard treatment alone. Two published studies, Campos et al. (described in the previous section) and Navari et al., made this comparison using dosages of aprepitant that were substantially different from those currently prescribed.

The Navari study was a multicenter, double-blind, placebo controlled trial involving 159 patients who had not previously received cisplatin that evaluated the prevention of acute emesis and delayed emesis after a single dose of cisplatin therapy (70 mg/$m^2$ or more). Before receiving cisplatin, all the patients received standard therapy: granisetron (10 mg/kg intravenously) and dexamethasone (20 mg orally). The patients were randomly assigned to one of three treatments in addition to granisetron and dexamethasone as outlined in Table 3. In the acute-emesis phase, 93 percent of the patients in Groups 1 and 2 combined and 67 percent of those in Group 3 had no vomiting ($p < 0.01$). In the delayed-emesis phase, 82 percent of the patients in Group 1, 78 percent of those in Group 2, and 33 percent of those in Group 3 had no vomiting ($p < 0.01$ for the comparison between Group 1 or 2 and Group 3). The median nausea score in the delayed-emesis phase was significantly lower in Group 1 than in Group 3 ($p < 0.01$).

**Table 3. Study by Navari et al.**

| Treatment | | | No Emesis | |
|---|---|---|---|---|
| Group | Day 1 | Days 2-5 | Day 1 | Days 2-5 |
| 1 | Std. Therapy plus Aprepitant 400mg | Aprepitant 300mg | 93 % | 82 % |
| 2 | Std. Therapy plus Aprepitant 400mg | Placebo | | 78 % |

| Table 3. Study by Navari et al. | | | | |
|---|---|---|---|---|
| | | | | |
| 3 | Std. Therapy only | Placebo | 67 % | 33 % |

The following Phase II and Phase III studies that were submitted to the FDA and led to the approval of aprepitant include dosages similar to the aprepitant dosage regimen in current use, 125 mg on the first day and 80 mg on the second and third days.

In a Phase II trial, Chawla et al. conducted a multicenter, randomized, double-blind, placebo-controlled study in patients with cancer who were receiving initial cisplatin (70mg/$m^2$ or more) and standard anti-emetic therapy (intravenous ondansetron plus oral dexamethasone). Patients were randomized to receive standard therapy plus either aprepitant 375 mg on Day 1 and 250 mg on Days 2–5, or aprepitant 125 mg on Day 1 and 80 mg on Days 2–5, or placebo. Due to an apparent interaction with dexamethasone suggested by pharmacokinetic data obtained while the study was ongoing, the aprepitant 375/250 mg dose was discontinued and replaced with aprepitant 40 mg on Day 1 and 25 mg on Days 2–5, and a new randomization schedule was generated. Patients recorded nausea and emesis in a diary. The primary endpoint was complete response (no emesis and no rescue therapy), which was analyzed using an intent-to-treat approach with data obtained after the dose adjustment.

| Table 4. Study by Chawla et al. | | | | | | |
|---|---|---|---|---|---|---|
| Treatment | | | | Complete Response | | |
| Group | Day 1 | Days 2-5 | N | Day 1 | Days 2-5 | Overall |
| 1 | Aprepitant 125mg and Std. Therapy | Aprepitant 80mg | 131 | 83.2 % | 72.7 % | 71.0 % |

| Table 4. Study by Chawla et al. | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | |
| 2 | Aprepitant 40mg and Std. Therapy | Aprepitant 25mg | 119 | 75.6 % | 63.9 % | 58.8 % |
| 3 | Std. Therapy | Placebo | 126 | 71.4 % | 45.2 % | 43.7 % |
| | | | | p< 0.05 for Group 1 vs. Group 3 | p< 0.01 for Group 1 or 2 vs. Group 3 | p< 0.05 for Group 1 or 2 vs. Group 3 |

There was a significant improvement in overall response in both aprepitant groups compared to the standard group. Group 1 had a significantly improved response over Group 3 on Day 1 and both groups had a significant improvement over Group 3 on Days 2-5. The efficacy of the aprepitant 375/250-mg regimen was similar to that of the aprepitant 125/80-mg regimen. The overall incidence of adverse events was generally similar across treatment groups: 85% in the aprepitant 375/250-mg group (34 patients), 76% in the aprepitant 125/80-mg group (214 patients), 71% in the aprepitant 40/25-mg group (120 patients), and 72% in the standard therapy group (212 patients), with the exception of a higher incidence of infection in the aprepitant 125/80-mg group (13%) compared with the standard therapy group (4%).

There are two published Phase III studies. Hesketh et al. randomized 520 patients who were receiving cisplatin (70mg/$m^2$ or more), half to standard therapy (ondansetron and dexamethasone on Day 1, and dexamethasone alone on Days 2-4) and half to the same therapy with the addition of aprepitant on Days 1-3. The percentages of patients with no emesis and no use of rescue therapy on Day 1, Days 2-5 and overall were, respectively, 89.2%, 75.4%, and 72.7% in the aprepitant group and 78.1%, 55.8%, and 52.3% in the standard therapy group ($p < 0.01$ for all comparisons between groups). Poli-Bigelli et al. published another Phase III study using the same protocol. During the 5 days after chemotherapy, the percentages of patients who achieved a complete response were 62.7% in the aprepitant group (163 of 260 patients) versus 43.3% in the standard therapy group (114 of 263 patients; $p < 0.01$). For Day 1, the complete response rates were 82.8% for the aprepitant group and 68.4% for the standard therapy group ($p < 0.01$); for Days 2–5, the complete response rates were 67.7% in the aprepitant group and 46.8% in the standard therapy group ($p < 0.01$).

| Table 5. Study by Hesketh et al. | | | | |
|---|---|---|---|---|
| Treatment | | Complete Response | | |
| Day 1 | Days 2-3 | Day 1 | Days 2-5 | Overall |
| Aprepitant 125mg and Std. Therapy | Aprepitant 80mg | 89.2 % | 75.4 % | 72.7 % |
| Std. Therapy | Placebo | 78.1 % | 55.8 % | 52.3 % |
| | | | | p< 0.01 |

| Table 6. Study by Poli-Bigelli et al. | | | | |
|---|---|---|---|---|
| Treatment | | Complete Response | | |
| Day 1 | Days 2-3 | Day 1 | Days 2-5 | Overall |
| Aprepitant 125mg and Std. Therapy | Aprepitant 80mg | 82.8 % | 67.7 % | 62.7 % |
| Std. Therapy | Placebo | 68.4 % | 46.8 % | 43.3 % |

| Table 6. Study by Poli-Bigelli et al. | | | | |
|---|---|---|---|---|
| | | | | |
| | | p< 0.01 | p< 0.01 | p< 0.01 |

DeWit et al. published two analyses (2003 and 2004) of the persistence of the efficacy of aprepitant in subsequent cycles of chemotherapy looking at the Phase II and Phase III studies. In the Phase II study, complete response rates for the aprepitant group were still 59% by cycle 6 but decreased to 34% for the standard therapy group. In the Phase III studies, rates of no emesis or significant nausea through cycle 6 were 59% with aprepitant and 40% with standard therapy.

**4. MCAC**

A Medicare Coverage Advisory Committee (MCAC) meeting was not convened on this issue.

**5. Evidence-based guidelines**

*NCCN Clinical Practice Guidelines (2004)*

The National Comprehensive Cancer Network (NCCN) publishes clinical practice guidelines for anti-emesis that consist of the authors' consensus of generally accepted treatment protocols. The 2004 guidelines recommend consideration of aprepitant use per the FDA-labeled indication for highly emetogenic chemotherapy regimens. Refer to the NCCN website for the authors' views of currently accepted approaches to anti-emesis treatment: http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf

The NCCN encourages cancer patients to participate in clinical trials for optimal case management.

*MASCC Clinical Guidelines (2004)*

Slides presented by the Multinational Association for Supportive Care In Cancer at the Consensus Conference on Anti-emetic Therapy in Perugia on March 29-31, 2004 include the following anti-emetic guidelines:

- Guideline for the Prevention of Acute Nausea and Vomiting Following Chemotherapy of High Emetic Risk:
  To prevent acute vomiting and nausea following chemotherapy of high emetic risk, a three-drug regimen including single doses of a 5-HT3 antagonist, dexamethasone, and aprepitant given before chemotherapy and a single dose of aprepitant and dexamethasone on Day 2 and Day 3 is recommended.
  - MASCC Level of Consensus: High
  - MASCC Level of Confidence: High

- Guideline for the Prevention of Delayed Nausea and Vomiting Following Chemotherapy of High Emetic Risk:
  In patients receiving cisplatin treated with a combination of aprepitant, a 5-HT3 antagonist and dexamethasone to prevent acute vomiting and nausea, the combination of dexamethasone and aprepitant is suggested to prevent delayed emesis, on the basis of its superiority to dexamethasone alone.
  - MASCC Level of Consensus: Moderate
  - MASCC Level of Confidence: High

*American Society of Clinical Oncology (ASCO 1999)*

ASCO guidelines recommend the use of 5-$HT_3$ antagonist and a corticosteroid for the prevention of acute chemotherapy-induced emesis. However, ASCO guidelines were created prior to FDA-approval of aprepitant and have yet to be updated.

*Authoritative Drug Compendia*

Citations from the drug compendia identified in §1861(t)(2)(B)(ii)(II) of the statute, the American Hospital Formulary Service-Drug Information (AHFS-DI) and the 2004 United States Pharmacopoeia-Drug Information (USP-DI), are listed below. The compendia should be consulted directly as information regarding drug usage changes as new evidence becomes available.

- AHFS-DI (2004)
  "Aprepitant is used in combination with other anti-emetic agents for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin therapy."
- USP-DI (2004)
  "Nausea and vomiting, cancer chemotherapy-induced (prophylaxis)-aprepitant, in combination with other anti-emetic agents, is indicated for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cancer chemotherapy."

## 6. Professional Society Position Statements

CMS received no professional society position statements.

## 7. Expert Opinion

CMS met with representatives for Merck & Co., Inc., manufacturer of aprepitant, to discuss available evidence.

**8. Public Comments**

*Initial public comments*

During the initial public comment period, CMS received written statements from four pharmaceutical companies, including the manufacturer of aprepitant, and statements from two physicians, a registered nurse and a cancer survivor.

One physician and the manufacturer of aprepitant supported a positive national coverage determination. Their comments are summarized below:

- The use of aprepitant in combination with a 5-HT3 antagonist and corticosteroid establishes a new oral regimen that is a full and complete replacement for earlier oral anti-emetic regimens for patients receiving highly emetogenic chemotherapy.
- NCCN and MASCC clinical guidelines endorse aprepitant as a standard of care for acute and delayed emesis for patients undergoing highly emetogenic chemotherapy.
- Aprepitant is the first FDA-approved oral anti-emetic of its type and is effective in both acute and delayed chemotherapy-induced emesis.

Comments from three additional pharmaceutical companies are summarized below:

- CMS does not have the legal authority to cover aprepitant as a full replacement for an intravenous anti-emetic because aprepitant is not effective as a stand-alone drug and does not have a one-to-one replacement for an intravenous anti-emetic drug.
- The NCCN and MASCC clinical guidelines do not recommend single agent therapy with aprepitant for prevention of acute chemotherapy-induced emesis.
- The FDA label insert cautions physicians prescribing aprepitant to patients receiving concomitant therapies (including chemotherapeutic agents) of potential adverse drug-to-drug interactions,

A physician and registered nurse commented that aprepitant is only mildly effective when given alone to prevent chemotherapy-induced emesis.

A cancer survivor who experienced an improvement in his quality of life commented on the importance of ensuring the availability of effective treatments.

Each of these comments has been considered and responses are incorporated into the CMS analysis below.

**VIII. CMS Analysis**

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage.

Section 1861(s)(2) includes in the definition of “medical and other health services” covered under Medicare Part B: an oral drug (which is approved by the Federal Food and Drug Administration) prescribed for use as an acute anti-emetic used as part of a chemotherapeutic regimen if the drug is administered by a physician (or as prescribed by a physician) –

i. for use immediately before, at, or within 48 hours after the time of the administration of the anticancer chemotherapeutic agent; and
ii. as a full replacement for the anti-emetic therapy which would otherwise be administered intravenously”

Moreover, with limited exceptions, the expenses incurred for items or services must be “reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.” § 1862(a)(1)(A).

Aprepitant is the first FDA-approved oral anti-emetic of its type. In keeping with our ongoing process to accommodate advances in medical technology and address emerging evidence, we analyzed the conditions under which the administration of aprepitant may act as a full replacement of the anti-emetic therapy that would otherwise be administered intravenously.

We addressed two conditions under which aprepitant might be considered as a full replacement for intravenous anti-emetic therapy, and as reasonable and necessary in the Medicare population.

1. *Is the quality of evidence adequate to conclude that aprepitant can function alone as a full replacement to intravenous anti-emetics and is reasonable and necessary for those Medicare patients who are receiving highly emetogenic chemotherapy.*

Aprepitant is not considered by clinicians to be a substitute for 5-$HT_3$ antagonist drugs and clinical guidelines explicitly state this conclusion. The mechanism of action of aprepitant is distinct from that of the 5-$HT_3$ antagonists. In the two clinical trials that substituted aprepitant for a 5-$HT_3$ antagonist for patients receiving cisplatin, subjects in the aprepitant group had more emesis on the first day and less emesis on subsequent days. This indicates that aprepitant is best used as a complementary agent with a 5-$HT_3$ antagonist and dexamethasone rather than as a replacement. We believe that the evidence is adequate to conclude that aprepitant cannot function alone as a full replacement for intravenously administered anti-emetic agents such as 5-$HT_3$ antagonists for patients who are receiving highly emetogenic chemotherapy and, therefore, is not reasonable and necessary for this indication.

2. *Is the quality of evidence adequate to conclude that aprepitant can function in combination with other oral anti-emetics as a full replacement to intravenous anti-emetics and is reasonable and necessary for that population of Medicare patients who is receiving highly emetogenic chemotherapy and who would otherwise fail on the standard oral anti-emetic regimen without aprepitant?*

We propose that the evidence is adequate to conclude that aprepitant cannot function alone as a full replacement for intravenously administered anti-emetic agents (such as 5-$HT_3$ antagonists) for patients who are receiving highly emetogenic chemotherapy. However, as demonstrated in Tables 3 through 6, when aprepitant is administered in combination with a 5-$HT_3$ antagonist and dexamethasone standard therapy regimen, the percentage of patients who achieve a complete response is increased over the percentage of patients receiving only standard therapy.

We believe that the evidence reviewed in this proposed decision memorandum has demonstrated that aprepitant administered in combination with standard oral anti-emetic therapy can constitute a full replacement of intravenous anti-emetic therapy for patients who fail on standard therapy alone.

## IX. Proposed Conclusion

CMS is seeking public comment on our proposed determination that there is sufficient evidence to conclude that the use of the oral anti-emetic three drug combination of aprepitant (Emend®), a 5-$HT_3$ antagonist, and dexamethasone is reasonable and necessary for a specified patient population.

For purposes of this proposed determination we are defining the patient population for which the use of the oral anti-emetic three drug combination of aprepitant (Emend®), a 5-$HT_3$ antagonist, and dexamethasone is reasonable and necessary as only those patients who:

- Are receiving anti-cancer chemotherapeutic agents defined as level 5 on Hesketh's classification system of acute emetogenicity of anti-cancer chemotherapeutic agents, and
- Have demonstrated unresponsiveness to other anti-emetic regimens not containing aprepitant that are consistent with nationally recognized guidelines associated with prior administration of the same chemotherapy.

We are requesting public comments on this proposed determination pursuant to section 731 of the Medicare Modernization Act. After considering the public comments and any additional evidence we will make a final determination and issue a final decision memorandum.

## APPENDIX A

### General Methodological Principles of Study Design
(Section VI of the Decision Memorandum)

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve net health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

**Assessing Individual Studies**

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

**Generalizability of Clinical Evidence to the Medicare Population**

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess net health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

**Assessing the Relative Magnitude of Risks and Benefits**

An intervention is not reasonable and necessary if its risks outweigh its benefits. Net health outcomes is one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

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